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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,739	HANNA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 1-46 and added new claims 47-68, which are related to claims 38-43, 45-46.

Accordingly, claims 47-68 are being examined.

The following are the remaining rejections.

New rejections Based on The Amendment

Objection

Claims 48-49, 66 is objected to for the use of the abbreviation language TGF or TGF-betaR. This objection could be obviated by amending claim 47 to which claims 48-49, 66 depend, for example, to recite "transformation growth factor-beta (TGF-beta)" and also by amending claims 48-49, 66 to recite "TGF-beta receptor-fusion protein" or "TGF-beta receptor-Fc-fusion protein".

Obviousness-type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 47-68 of the instant application are non-provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-2, 4-19 of US Application Serial No. 09/853581, now US patent No. 6,998,125.

The followings are the claims 47-68 of the instant application:

Claim 47 is drawn to a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation

comprising a human papillomavirus E7 protein, that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein, and a therapeutic effective amount of at least "one agent" that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta.

Claim 48 is drawn to the method of claim 47, wherein the agent is an anti-TGF beta antibody, a TGF beta R-fusion protein, "a TGF-beta analog", "a TGF beta binding protein", or a TGF-beta R blocking antibody.

Claim 49 is drawn to the agent is a thrombospondin peptide or a TGF-beta R- Fc fusion protein.

Claims 50-51 are drawn to the method of claim 47, wherein the cancer cells are cervical cancer cells (claim 50), or wherein the adjuvant formulation and at least one agent are administerered sequentially or concurrently, and in any order (claim 51).

Claim 52 is drawn to the method of claim 47, wherein the antigen-containing adjuvant formulation is a microfluidized antigen formulation comprising: (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion.

Claims 53-54 are drawn to the method of claim 52, wherein the detergent is provided in an amount ranging from approximately 0.05 to 0.5% (claim 53), or wherein the amount of detergent is about 0.2% (claim 54).

Claim 55 is drawn to the method of claim 52, wherein the detergent is selected from the group consisting of sorbitan-mono-g-octadecenoate-polytoxyl-l,z-ethanediyl, polyoxyethylene-sorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, polyoxyethylenesorbitan

monostearate, N-dodecyl-N,N-dimethyl-3-ammonio-l-propanesulfonate, alkyl (C9-C13) sodium sulfates, and sorbitan trioleate.

Claims 56-58 are drawn to the method of claim 52, wherein the micelle-forming agent has a hydrophile-lipophile balance of between 0 and 2 (claim 56), or wherein the amount of the micelle-forming agent ranges from 0.5 to 10% (claim 57), or from l .25 to 5% (claim 58).

Claims 59-61 are drawn to the method of claim 52, wherein the amount of oil ranges from 1 to 10% (claim 59), or from 2.5 to 5% (claim 60), or wherein the oil exhibits a melting temperature of less than 65^0 C (claim 61).

Claim 62 is drawn to the method of claim 52, wherein the oil is selected from the group consisting of squalane, eicosane, tetratetracontane, pristane, and vegetable oils.

Claim 63 is drawn to the method of claim 52, wherein the antigen formulation comprises sorbitan-mono-g-octadecenoate-polytoxyl-l,z-ethanediyl, block copolymer having the structure:

$$HO(CH_2CH_2O)a\text{-}(\underset{\substack{|\\ CH3}}{CH}CH_2O)b\text{-}(CH_2CH_2O)aH,$$

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane.

Claims 64-65 are drawn to the method of claim 52, wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide (claim 64), or wherein the antigen formulation lacks an immunostimulating muramyl dipeptide (claim 65).

Claim 66-67 are drawn to the method of claim 52, wherein the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of

TGFj is selected from the group consisting of an anti-TGF-beta antibody, a TGF-beta R-fusion protein, a TGF beta analog, a TGFP binding protein, and a TGF-beta R blocking antibody (claim 66), and wherein the cancer cells are cervical cancer cells (claim 67).

Claim 68 is drawn to the method of claim 52, wherein the antigen-containing adjuvant formulation and at least one agent of step (b) are administered sequentially or concurrently, and in any order.

The followings are the claims 1-2, 4-19 of US Application Serial No. 09/853581, now US patent No. 6,998,125.

Claim 1 is drawn to a method of treating cancer comprising administering to a patient in need thereof: (a) an admixture comprising a cancer or tumor antigen expressed by cells of the cancer to be treated and a microfluidized antigen formulation comprising: (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion; wherein said admixture is administered to said patient in an amount sufficient to induce a cytotoxic T-lymphocyte response in said patient which is specific for the cancer or tumor antigen contained in said admixture, and (b) a therapeutically effective amount of at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor .beta. (TGF.beta.) specifically, which agent is selected from the group consisting of an anti-TGF.beta. antibody, a TGF.beta.R-fusion protein, a TGF.beta. analog, a TGF.beta. binding protein, and a TGF.beta.R blocking antibody; wherein the antigen-containing admixture and the at least one agent which is capable of neutralizing, blocking,

antagonizing, or down regulating the activity or preventing activation of TGF.beta. are administered sequentially or concurrently, and in any order.

Claim 2 is drawn to the method of claim 1, wherein the antigen-containing admixture and the at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGF.beta. are administered sequentially.

Claim 4 is drawn to the method of claim 1, wherein the at least one agent which is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGF.beta. is a thrombospondin peptide or a TGF.beta.R Fc-fusion protein.

Claim 5 is drawn to the method of claim 1, wherein the admixture comprises a cancer or tumor antigen selected from the group consisting of gp100, MART-1/Melan A, gp75, tyrosinase, melanoma prateoglycan, MAGE, BAGE, GAGE, RAGE, N-acetylglucosaminyltransferase-V, mutated B-catenin, mutated MUM-1, mutated cyclin dependent kinases-4, p21 ras, BCR-abl, p53, p185 HER2/neu, mutated epidermal growth factor receptor, carcinoembryonic antigens, carcinoma associated mutated mucins, Epstein Barr nuclear antigen (EBNA) gene products, **papillomavirus E7 protein**, papillomavirus E6 protein, prostate specific antigens, prostate specific membrane antigen, and prostate carcinoma tumor antigen-1 (PCTA-1).

Claim 6 is drawn to the method of claim 1, wherein the cancer is selected from the group consisting of breast cancer, brain cancer, cervical cancer, leukemia, lymphoma, prostate cancer, skin cancer, colon cancer, lung cancer, ovarian cancer, pancreatic cancer, liver cancer, bladder cancer, kidney cancer, myeloma, colorectal cancer, nasopharyngial carcinoma, or endometrial cancer.

Claim 7 is drawn to the method of claim 1, wherein the detergent is provided in an amount ranging from approximately 0.05 to 0.5%.

Claim 8 is drawn to the method of claim 7, wherein the amount of detergent is about 0.2%.

Claim 9 is drawn to the method of claim 1, wherein the detergent is selected from the group consisting of sorbitan-mono-9-octadecenoate-poly(oxy)-1,2-ethanediy- l, polyoxyethylenesorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, polyoxyethylenesorbitan monostearate, N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, alkyl (C.sub.9 C.sub.13) sodium sulfates, and sorbitan trioleate.

Claim 10 is drawn to the method of claim 1, wherein the micelle-forming agent has a hydrophile-lipophile balance of between 0 and 2.

Claim 11 is drawn to the method of claim 1, wherein the amount of the micelle-forming agent ranges from 0.5 to 10%.

Claim 12 is drawn to the method of claim 11, wherein the amount of the micelle-forming agent ranges from 1.25 to 5%.

Claim 13 is drawn to the method of claim 1, wherein the amount of oil ranges from 1 to 10%.

Claim 14 is drawn to the method of claim 13, wherein the amount of oil ranges from 2.5 to 5%.

Claim 15 is drawn to the method of claim 1, wherein the oil exhibits a melting temperature of less than 65 degree C.

Claim 16 is drawn to the method of claim 1, wherein the oil is selected from the group consisting of squalane, eicosane, tetratetracontane, pristane, and vegetable oils.

Claim 17 is drawn to the method of claim 1, wherein the antigen-containing admixture comprises sorbitan-mono-9-octadecenoate-poly(oxy)-1,2-ethanediyl, a block copolymer having the structure:

$HO(CH_2CH_2\,O)a\text{-}\ (CHCH_2\,O)b\text{-}(CH_2CH_2O)aH,$
1
CH3

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane.

Claim 18 is drawn to the method of claim 1, wherein the antigen-containing admixture contains no more than 20 micrograms of an immunostimulating muramyl dipeptide.

Claim 19 is drawn to the method of claim 1, wherein the antigen-containing admixture lacks an immunostimulating muramyl dipeptide.

The combined methods of claims 1-2, 4-19 of US 6,998,125 have all the limitations of the methods as claimed in claims 47-50, 52-68 of the instant invention. Further, it would have been obvious to administer the composition taught by US 6,998,125 sequentially or concurrently, and in any order, as claimed in claim 51 of the instant invention, to increase the versatility of the treatment method. Thus, although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept.

It is noted that an obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct

from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

This is a non-provisional obviousness-type double patenting rejection because the conflicting claims have in fact been patented.

Claim Rejections - 35 USC § 112 First Paragraph, New matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 64 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response, wherein the antigen formulation **contains no more than** 20 micrograms of an immunostimulatory muramyl dipeptide claimed in Claim 64 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for "It is important in the above formulation that a peptide component, especially a muramyl dipeptide be lacking. Such peptide will interfere with induction of a CTL response if it provided in an amount greater than about 20

micrograms per normal human formulation administration.....That is although such peptides may enhance the humoral response, they are disadvantageous when a cytotoxic T-lymphocyte response is desired" (p.12, second paragraph).

The specification only teaches not to use the muramyl dipeptide, and its properties, i.e. it will interfere with induction of a CTL response if it provided in an amount greater than about 20 micrograms. There is nothing in the specification to teach or suggest to **use** an antigen formulation containing no more than 20 micrograms of an immunostimulatory muramyl dipeptide in the claimed method for enhancing an antigen-specific cytotoxic T cell lymphocyte. The subject matter claimed in claim 46 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63-65 recite the limitation "the antigen formulation" in claim 52. There is insufficient antecedent basis for this limitation in the claim 52, which recites "an adjuvant formulation".

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-48, 50-65, 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 47 is drawn to a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein, that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein, and a therapeutic effective amount of at least "one agent" that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta.

Claim 48 is drawn to the method of claim 47, wherein the agent is an anti-TGF beta antibody, a TGF beta R-fusion protein, "a TGFbeta analog", "a TGF beta binding protein", or a TGFbeta R blocking antibody.

Claims 50-51 are drawn to the method of claim 47, wherein the cancer cells are cervical cancer cells (claim 50), or wherein the adjuvant formulation and at least one agent are administerered sequentially or concurrently, and in any order (claim 51).

Claim 52 is drawn to the method of claim 47, wherein the antigen-containing adjuvant formulation is a microfluidized antigen formulation comprising: (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion.

Claims 53-54 are drawn to the method of claim 52, wherein the detergent is provided in an amount ranging from approximately 0.05 to 0.5% (claim 53), or wherein the amount of detergent is about 0.2% (claim 54).

Claim 55 is drawn to the method of claim 52, wherein the detergent is selected from the group consisting of sorbitan-mono-9-octadecenoate-polytoxyl-1,2-ethanediyl, polyoxyethylene-sorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, polyoxyethylenesorbitan monostearate, N-dodecyl-N,N-dimethyl-3-ammonio-l-propanesulfonate, alkyl (C9-C13) sodium sulfates, and sorbitan trioleate.

Claims 56-58 are drawn to the method of claim 52, wherein the micelle-forming agent has a hydrophile-lipophile balance of between 0 and 2 (claim 56), or wherein the amount of the micelle-forming agent ranges from 0.5 to 10% (claim 57), or from l .25 to 5% (claim 58).

Claims 59-61 are drawn to the method of claim 52, wherein the amount of oil ranges from 1 to 10% (claim 59), or from 2.5 to 5% (claim 60), or wherein the oil exhibits a melting temperature of less than 65^0 C (claim 61).

Claim 62 is drawn to the method of claim 52, wherein the oil is selected from the group consisting of squalane, eicosane, tetratetracontane, pristane, and vegetable oils.

Claim 63 is drawn to the method of claim 52, wherein the antigen formulation comprises sorbitan-mono-9-octadecenoate-polytoxyl-1,2-ethanediyl, block copolymer having the structure:

$$HO(CH_2CH_2O)a\text{-}(\underset{\displaystyle CH3}{\overset{}{CH}}CH_2O)b\text{-}(CH_2CH_2O)aH,$$

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane.

Claims 64-65 are drawn to the method of claim 52, wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide (claim 64), or wherein the antigen formulation lacks an immunostimulating muramyl dipeptide (claim 65).

Claim 68 is drawn to the method of claim 52, wherein the antigen-containing adjuvant formulation and at least one agent of step (b) are administered sequentially or concurrently, and in any order.

It is noted that "**agent**" that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta (TGF beta encompasses a genus of antagonists of TGF beta, having unknown structure, for example, **any antagonist peptide or non-peptide mimetics, or any small molecule antagonists.**

Further, "**TGF beta analog**" encompasses **a genus of antagonist variants of TGF beta, having unknown structure.**

In addition, TGF-beta binding protein encompasses **a genus of antagonist proteins of unknown structure that bind to TGF-beta.**

It is further noted that the disclosed anti-TGF-beta antibody, anti-TGF-beta receptor antibody, TGF-beta receptor-Fc fusion protein, and thrombospondin are **not representative species,** because they do not have common structure. Further, the specification does not disclose

a correlation between structure and function, which structure feature constitutes a substantial portion of the genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe the TGF-beta antagonist agent, TGF-beta analog, or TGF beta binding protein, in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide sufficient structure or common structure, other than anti-TGF-beta antibody, anti-TGF-beta receptor antibody, TGF-beta receptor-Fc fusion protein, and thrombospondin, to support the broad breath of the claimed genus. Nor is there any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses anti-TGF-beta antibody, anti-TGF-beta receptor antibody, TGF-beta receptor-Fc fusion protein, and thrombospondin, this

does not provide a description of the TGF-beta antagonist agent, TGF-beta analog, or TGF beta binding protein that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe the TGF-beta antagonist agent, TGF-beta analog, or TGF beta binding protein, by the standards shown in the example in Lilly. The specification describes only anti-TGF-beta antibody, anti-TGF-beta receptor antibody, TGF-beta receptor-Fc fusion protein, and thrombospondin. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Further, it is noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004), the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them". The present application is similar to that in *Rochester* case, in that although the structure of TGF-beta and TGF-beta receptor is known in the art, and except for antibody inhibitors of TGF-beta and TGF-beta receptor, TGF-beta receptor-Fc fusion protein, and thrombospondin, one cannot predict what mimetics or which small molecules might bind to and inactivate TGF-beta, especially in view that three dimensional structure of TGF-beta or TGF-beta receptor is not even disclosed in the specification or known in the art

The specification does not provide an adequate written description of the TGF-beta antagonist agent, TGF-beta analog, or TGF beta binding protein, that is required to practice the claimed invention. Thus, the specification does not meet the 112, first paragraph written

description requirement, and one of skill in the art would reasonably conclude that Applicant did not have possession of the antagonist agent, TGF-beta analog, or TGF beta binding protein at the time the invention was made. Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method.

Claim Rejections - 35 USC § 112, First Paragraph, Scope

Claims 47-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cervical cancer, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein, and an antagonist antibody against TGF-beta, a TGF-beta receptor fusion protein, or a TGF-beta receptor-Fc fusion protein, does not reasonably provide enablement for a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against "**cancer cells**", comprising administering a human papillomavirus E7 protein, and at least one **agent** that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta, a **TGF-beta analog**, a **TGF-beta binding protein**, or a **full length thrombospondin** peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 47 is drawn to a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein, that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein, and a therapeutic

effective amount of at least "one agent" that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta.

Claim 48 is drawn to the method of claim 47, wherein the agent is an anti-TGF beta antibody, a TGF beta R-fusion protein, "a TGF-beta analog", "a TGF beta binding protein", or a TGF-beta R blocking antibody.

Claim 49 is drawn to the agent is a thrombospondin peptide or a TGF-beta R- Fc fusion protein.

Claims 50-51 are drawn to the method of claim 47, wherein the cancer cells are cervical cancer cells (claim 50), or wherein the adjuvant formulation and at least one agent are administerered sequentially or concurrently, and in any order (claim 51).

Claim 52 is drawn to the method of claim 47, wherein the antigen-containing adjuvant formulation is a microfluidized antigen formulation comprising: (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion.

Claims 53-54 are drawn to the method of claim 52, wherein the detergent is provided in an amount ranging from approximately 0.05 to 0.5% (claim 53), or wherein the amount of detergent is about 0.2% (claim 54).

Claim 55 is drawn to the method of claim 52, wherein the detergent is selected from the group consisting of sorbitan-mono-g-octadecenoate-polytoxyl-l,z-ethanediyl, polyoxyethylene-sorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, polyoxyethylenesorbitan monostearate, N-dodecyl-N,N-dimethyl-3-ammonio-l-propanesulfonate, alkyl (C9-C13) sodium sulfates, and sorbitan trioleate.

Claims 56-58 are drawn to the method of claim 52, wherein the micelle-forming agent has a hydrophile-lipophile balance of between 0 and 2 (claim 56), or wherein the amount of the micelle-forming agent ranges from 0.5 to 10% (claim 57), or from l .25 to 5% (claim 58).

Claims 59-61 are drawn to the method of claim 52, wherein the amount of oil ranges from 1 to 10% (claim 59), or from 2.5 to 5% (claim 60), or wherein the oil exhibits a melting temperature of less than 65^0 C (claim 61).

Claim 62 is drawn to the method of claim 52, wherein the oil is selected from the group consisting of squalane, eicosane, tetratetracontane, pristane, and vegetable oils.

Claim 63 is drawn to the method of claim 52, wherein the antigen formulation comprises sorbitan-mono-g-octadecenoate-polytoxyl-l,z-ethanediyl, block copolymer having the structure:

$$HO(CH_2CH_2O)a\text{-}\underset{\underset{CH3}{|}}{(CHCH_2O)}b\text{-}(CH_2CH_2O)aH,$$

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane.

Claims 64-65 are drawn to the method of claim 52, wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide (claim 64), or wherein the antigen formulation lacks an immunostimulating muramyl dipeptide (claim 65).

Claim 66-67 are drawn to the method of claim 52, wherein the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFj is selected from the group consisting of an anti-TGF-beta antibody, a TGF-beta R-fusion

protein, a TGF beta analog, a TGFP binding protein, and a TGF-beta R blocking antibody (claim 66), and wherein the cancer cells are cervical cancer cells (claim 67).

Claim 68 is drawn to the method of claim 52, wherein the antigen-containing adjuvant formulation and at least one agent of step (b) are administered sequentially or concurrently, and in any order.

The following *Wands* factors have been considered when the 112, first paragraph, enablement rejection was made:

The breadth of the claims

The breadth of the claims is broad, encompassing a method for enhancing CTL response or treating *any* cancer, using the human papillomavirus E7 protein and a genus of antagonists of TGF-beta, a genus of TGF-beta analogs, or a genus of TGF-beta binding protein, the structure of which antagonists, analogs, or binding proteins is not known. The claims also encompass a method for enhancing CTL response or treating cancer, using the human papillomavirus E7 protein and the **full length** thrombospondin protein.

The nature of the invention

The nature of the invention is complex.

The state of the prior art

Although the prior art teaches a method for treating a cancer in mice inoculated with a cancer cell line that expresses HPV 16 E7 gene, using a composition comprising HPV 16 E7

antigen (see 103 Rejection below), the art does not teach a method for treating **any** cancer, using the HPV 16 E7 antigen. Further, the art only teaches specific antagonists of TGFbeta, such as anti-TGF-beta antibody, or TGF-beta receptor fused to Fc (see 103 Rejection below). In addition, although the art teaches that a specific peptide from thrombospondin, GGWSHW, **inactivates** TGF-beta, the art teaches that the full length thrombospondin actually has the opposite effect, i.e. **activating** TGF-beta (Schultz-Cherry et al, 1995, JBC, 270 (13): 7304-7310, see abstract).

The level of one of skill in the art

Although the level of skill in the field of molecular pathology is high, it would be undue experimentation for one of skill in the art to practice the claimed invention.

The level of predictability of the art

The level of unpredictability in the art is high.

One cannot predict that any cancer would be treated with the HPV E7 antigen and an antagonist of TGF-beta, because not any cancer cells would express HPV E7, and thus the CTLs produced that are specific for HVP E7 would not predictably lyse any cancer cells. In addition, one cannot predict the structure of the claimed numerous agents that would be antagonists of TGF-beta, for example, which mimetics, or which small molecules inhibit the activity of TGF-beta. Similarly, one cannot predict which TGF-beta analog, or which TGF-beta binding protein would be an antagonist of TGF-beta, in view that not any TGF-beta analog, or not any TGF-beta binding protein would inhibit the activity of TGF-beta. Further, one cannot predict which of the fragment of thrombospondin protein other than GGWSHW, would **inhibit** TGF-beta activity,

because the full length thrombospondin actually has the opposite effect, i.e. **activating** TGF-beta, and because not any fragment of a protein would predictably have the opposite activity of the full length protein thereof.

Working example and The amount of direction provided by the inventor

The specification only discloses treating mice inoculated with cancer cells expressing HPV-E7, using a composition comprising the HPV E7 and anti-TGF-beta antibodies (Example 2 on pages 17-18). Other than anti-TGF-beta antibody, GF-beta receptor fused to Fc, and TGF-beta receptor blocking antibody, the specification does not disclose how to make the claimed numerous agents that inhibit TGF-beta, such as mimetics or small molecules antagonist of TGF-beta. The specification does not disclose which of the numerous claimed TGF-beta analogs or TGF-beta binding proteins inhibit the activity of TGF-beta.

It is noted that although screening method for antagonist is routine in the art, screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

It is further noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known

in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 47-48, 50-63, 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05).

Claim 47 is drawn to a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein, that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein, and a therapeutic effective amount of at least one agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor beta.

Claim 48 is drawn to the method of claim 47, wherein the agent is an anti-TGF beta antibody, a TGF beta R-fusion protein, a TGF-beta analog, a TGF beta binding protein, or a TGF-beta R blocking antibody.

Claims 50-51 are drawn to the method of claim 47, wherein the cancer cells are cervical cancer cells (claim 50), or wherein the adjuvant formulation and at least one agent are administerered sequentially or concurrently, and in any order (claim 51).

Claim 52 is drawn to the method of claim 47, wherein the antigen-containing adjuvant formulation is a microfluidized antigen formulation comprising: (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion.

Claims 53-54 are drawn to the method of claim 52, wherein the detergent is provided in an amount ranging from approximately 0.05 to 0.5% (claim 53), or wherein the amount of detergent is about 0.2% (claim 54).

Claim 55 is drawn to the method of claim 52, wherein the detergent is selected from the group consisting of sorbitan-mono-9-octadecenoate-polytoxyl-1,2-ethanediyl, polyoxyethylene-sorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, polyoxyethylenesorbitan monostearate, N-dodecyl-N,N-dimethyl-3-ammonio-l-propanesulfonate, alkyl (C9-C13) sodium sulfates, and sorbitan trioleate.

Claims 56-58 are drawn to the method of claim 52, wherein the micelle-forming agent has a hydrophile-lipophile balance of between 0 and 2 (claim 56), or wherein the amount of the micelle-forming agent ranges from 0.5 to 10% (claim 57), or from l .25 to 5% (claim 58).

Claims 59-61 are drawn to the method of claim 52, wherein the amount of oil ranges from 1 to 10% (claim 59), or from 2.5 to 5% (claim 60), or wherein the oil exhibits a melting temperature of less than 65^0 C (claim 61).

Claim 62 is drawn to the method of claim 52, wherein the oil is selected from the group consisting of squalane, eicosane, tetratetracontane, pristane, and vegetable oils.

Claim 63 is drawn to the method of claim 52, wherein the antigen formulation comprises sorbitan-mono-9-octadecenoate-polytoxyl-1,2-ethanediyl, block copolymer having the structure:

$$HO(CH_2CH_2O)a\text{-}\underset{\underset{CH3}{|}}{(CHCH_2O)}b\text{-}(CH_2CH_2O)aH,$$

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane.

Claim 65 is drawn to the method of claim 52, wherein the antigen formulation lacks an immunostimulating muramyl dipeptide (claim 65).

Claim 66-67 are drawn to the method of claim 52, wherein the agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of TGFj is selected from the group consisting of an anti-TGF-beta antibody, a TGF-beta R-fusion protein, a TGF beta analog, a TGFP binding protein, and a TGF-beta R blocking antibody (claim 66), and wherein the cancer cells are cervical cancer cells (claim 67).

Claim 68 is drawn to the method of claim 52, wherein the antigen-containing adjuvant formulation and at least one agent of step (b) are administered sequentially or concurrently, and in any order.

US 5,695,770 teaches a method for inducing a cytotoxic T cells response (CTL) , or treating cervical cancer, comprising administering a therapeutically effective amount of a composition comprising a human papillomavirus antigen, HPV 16 E7 antigen, mixed with a

microfluidized antigen formulation comprising (a) a stabilizing detergent, (b) a micelle-forming agent, and (c) a biodegradable and biocompatible oil (claims 1-3 and Example 11 on columns 18-20). US 5,695,770 teaches that the detergent is TWEEN 20, TWEEN 40, TWEEN 80, ZWITTERGENT 3-12, TEEPOL HB7 or SPAN 85, and the oil is squalane, eicosane, pristane, peanut oil or other vegetable oil (claims 5-7, column 5, second paragraph), and the micelle-forming agent is polyoxamer 401 (claim 6). US 5,695,770 teaches that the detergent polysorbate 80 is TWEEN 80, or sorbitan-mono-9-octadecenoate-polytoxyl-1,2-ethanediyl, and that the detergent is usually provided in an amount of approximately 0.05 to 0.5%, preferably at about 2% (column 4, lines 44-52). US 5,695,770 teaches that preferably, the micelle-forming agent is chosen to have a hydrophilic-lipophile balance of between 0 and 2, and in amount between 0.5% and 10%, and most preferably between 1.25 and 5% (column 4, last paragraph, bridging column 5). US 5,695,770 teaches that the oil preferably has a melting temperature of less than 65 degree C, and provided in an amount between 1 and 10%, most preferably between 2.5 and 5% (column 5, second paragraph). US 5,695,770 teaches that the method lacks an immunostimulating peptide, such as muramyl dipeptide, the presence of which would decrease the desired cellular response (column 3, lines 64-67).

US 5,695,770 does not teach a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein and an inhibitor of TGF-beta, which could be an anti-TGF-beta antibody, a TGF-beta R-fusion protein, a TGF-beta binding protein or a TGF-beta R blocking antibody.

WO 94/09815 teaches a method for increasing the effectiveness of a vaccine comprising administering to an individual about to receive a vaccine or receiving a vaccine a TGF-beta receptor fragment that binds to TGF-beta to reduce excess TGF-beta activity and to increase the immune response to the vaccine in the individual (p.6, paragraph before last, claim 19, Example 3 on pages 27-28). WO 94/09815 teaches that antibody specific for TGF-beta has also been used in the art to suppress the activity of TGF-beta, and to counteract the immunosuppressive effects of TGF-beta (p.2, second paragraph).

Woodworth et al teach that contrary to normal anogenital epithelia, immortalized cervical carcinoma cell lines expressing HPV E6 and E7 are stimulated by TGF-beta, when cultured under conditions promoting squamous differentiation, although both normal and the immortalized cell lines express comparable level of TGF-beta receptors (abstract, p.815, p.816, second column, p.817, second paragraph). Woodworth et al teach that these in vitro observations suggest how altered responsiveness to TGF-beta might contribute to unregulated growth of HPV-imortalized cells in vivo (p.816, second column).

It would have been prima facia obvious at the time the invention was made to enhance a CTL response in cancer cells, such as cervival cancer cells, using a combined composition comprising a human papillomavirus antigen, HPV 16 E7 antigen, taught by US 5,695,770, with an inhibitor of TGF-beta, such as a TGF-beta receptor fragment that binds to TGF-beta, or an anti-TGF-beta antibody, as taught by WO 94/09815, because a combination of an inhibitor of TGF-beta and a vaccine, as taught by WO 94/09815, increases the immune response to the vaccine, and counteract the immunosuppressive effects of TGF-beta, as taught by WO 94/09815, and because growth of cancer cells lines that express HPV E7 are stimulated by TGF-beta, as

taught by Woodworth et al. Further, it would have been obvious to administer the composition taught by the combined art sequentially or concurrently, and in any order, as claimed in claim 51 of the instant invention, to increase the versatility of the treatment method.

It is noted that the micelle-forming agent polyoxamer 401 as taught by US 5,695,770 (claim 8 of US 5,695,770) is a block copolymer having the structure:

$$HO(CH_2CH_2O)a\text{-}\underset{\underset{CH3}{|}}{(CHCH_2O)}b\text{-}(CH_2CH_2O)aH,$$

wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000 and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks, and squalane, as evidenced by Schomolka et al (Schomolka et al, figure 1, p.110, table 1 on page 112), and as admitted by Applicant on page 9, third paragraph, of the response of 06/30/06.

B. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05), and further in view of Schultz-Cherry et al, 1995 (JBC, 270 (13): 7304-7310) or Capon DJ et al (WO 91/08298).

Claim 49 is drawn to the method of claim 47, wherein the agent is a thrombospondin peptide or a TGF-beta R- Fc fusion protein.

The teaching of US 5,695,770, Woodworth et al, WO 94/09815, Schmolka et al has been set forth above.

US 5,695,770, Woodworth et al, Capon et al, WO 94/09815, and Schmolka do not teach a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cancer cells, comprising administering an adjuvant formulation comprising a human papillomavirus E7 protein and a therapeutically effective amount of a thrombospondin peptide or a TGF-beta R- Fc fusion protein.

Schultz-Cherry et al teach that an hexapeptide fragment of thrombospondin protein, GGWSHW, binds to TGF-beta, and inhibits the activation of latent TGF-beta, by inhibiting the interaction of TGF-beta with its activator TSP1 (abstract).

WO 91/08298 teaches a TGF-beta inhibitor comprising a TGF-beta receptor linked to a constant region of an immunoglobulin (p.2, lines 15-20, p.25, last paragraph bridging p.26). WO 91/08298 teaches that the improved inhibitors should have much lower molecular weight and higher affinity than anti-TGF-beta antibodies, and that the TGF-beta receptor linked to a constant region of an immunoglobulin is preferable as compared to anti-TGF-beta antibodies because of their small size as compared to the antibodies (p.2, second paragraph, p.44, last paragraph).

It would have been obvious to replace the anti-TFG-beta antibodies in the method taught by US 5,695,770, Woodworth et al, Capon et al, WO 94/09815, and Schmolka with another TGF-beta antagonist, such as the thrombospondin peptide GGWSHW taught by Schultz-Cherry et al or a TGF-beta receptor linked to a constant region of an immunoglobulin, taught by WO 91/08298, because using the thrombospondin peptide GGWSHW or the TGF-beta receptor

linked to a constant region of an immunoglobulin provides alternative treatment methods, and thus increasing the versatility of the treatment methods.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 17, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER